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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/720,006	KARL ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-48,73,75-77,81 and 82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-48,73,75-77,81 and 82* is/are rejected.

7)☒ Claim(s) *44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment, filed 4/5/2010, is acknowledged and has been entered.

2. Claim 44 was amended. New claims 83-93 have been added. Accordingly, claims 44-48, 73, 75-77, and 81-93 are currently pending and subject to examination below.

Objections/ Rejections Withdrawn

3. The rejections of claims 44-48, 73, 75-77 and 81-82 under § 112, 1st and 2nd paragraphs as set forth in the previous Office action have been withdrawn in response to Applicant's amendments to claim 44 to remove step (d).

4. The rejections of claims 44, 46-48, 73, 76-77, and 81 under § 103(a) based upon Karl et al. (WO 99/05525) have been withdrawn in response to Applicant's amendments to claim 44 to remove step (d), such that the claims are now entitled to the benefit of prior-filed foreign application No. 198 38 802.0, filed 8/26/1998. The Karl et al. reference, with a publication date of 2/4/1999, no longer constitutes prior art.

5. The rejections of claims 44-45, 47-48, 73, 75-77, and 81 under § 103 as being unpatentable over O'Connor et al. in view of Osther et al. and either one of Bayer et al. or Tidey et al. have been withdrawn in favor of the rejections set forth below based upon O'Connor et al. in view of Osther et al. alone. In particular, Applicant's amendments to claim 44 to remove limitations of step (d) broaden the scope of the claims such that the teachings of Bayer et al. and Tidey et al. are no longer necessary in the obvious analysis.

Claim Objections

6. Claim 44 is objected to because of the following informalities:

In the prior version of the claim, the preamble concluded "…antibodies specific for the proteins, the method comprising the steps of". In the currently amended claims, the separating comma has apparently been removed. Applicant is requested to reintroduce the comma for clarity. Applicant is also reminded that when changes are made to the claims, as in the deletion of the comma here, such changes must be indicated through the use of appropriate markings. See MPEP 714.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 83-93 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of detecting a plurality of analytes in a sample; or alternatively for methods of detecting a pathogen by detecting a plurality of those analytes that are proteins of a pathogen or antibodies specific for the proteins; does not reasonably provide enablement for methods of detecting a pathogen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Newly added claim 83 recites a method for detecting a pathogen by detecting a plurality of analytes in a sample. In contrast to independent claim 44, which requires that the analytes detected are either proteins of the pathogen or antibodies to the proteins, claim 83 requires that the analytes are those that "stem from the pathogen or are induced thereby".

Claim 83 therefore broadly encompasses diagnostic methods for detecting a pathogen by detecting <u>any</u> antigen or antibody that stems from the pathogen or is induced thereby. Such antigens or antibodies would include proteins of the pathogen and antibodies specific for the proteins, as recited in instant claim 44. However, claim 83 is not limited to pathogen proteins and antibodies thereto, but also encompasses antigens or antibodies that could be, for example, human proteins that are normally expressed in blood but which are elevated in response to infection by a pathogen.

However, the fact that a marker is elevated in the disease state does not necessarily mean that the marker may be used for the purpose of diagnosing that disease.

One skilled in the art would recognize that in order to be employed in diagnosis, a biomarker must be *specific* to the disease to be diagnosed. See for example Mayeux et al. ("Biomarkers: Potential uses and Limitations"; NeuroRx (2004); Vol. 1, pages 182-188), which teaches that biomarkers are validated by a number of criteria, including the extent to which the biomarker correlates with the specific disease under study (page 186, left column, the first full paragraph).

LaBaer et al. (Journal of Proteome Research (2005), Vol. 4, pages 1053-1059) teach that in general, much higher demands are placed on biomarkers to be used for diagnosis, and that quantitative values must be established in order to set the boundary between a positive and a

negative test (see the paragraph bridging the left and right columns of page 1054). LaBaer et al. further teach that as a result, this requires that the measurements for individuals without the disease exhibit relatively little variation, since otherwise, establishing a cutoff value will be difficult (ibid). This scenario is depicted in Figure 5 of LaBaer et al. (see also p. 1056-1057), where it can be seen that if the mean values for healthy and disease populations overlap, it is difficult to establish a cutoff value that would separate the two populations.

In the instant case, antigens or antibodies that "stem from [a] pathogen or are induced thereby" would not necessarily be specific to the pathogen. In other words, infection by a pathogen may cause elevation in markers that are also elevated in the context of other, disparate disease states.

For example, the prior art recognized that the marker lactate dehydrogenase (LDH) is elevated upon HIV infection, such that it would be considered an antigen that "stems from" or is "induced" by the pathogen HIV. See The Nemours Foundation, "Blood Test: Lactate Dehydrogenase (LDH)", January 2009, retrieved from http://kidshealth.org/parent/system/medical/test_ldh.html on 6/14/2010. However, LDH levels can be elevated for a variety of reasons, including cancer. See "Symptoms and Diagnosis of Cancer", the Merck Manuals Online Medical Library Home Edition, October 2006, 5 pages, retrieved from http://www.merck.com/mmhe/sec15/ch181/ch181c.html on 6/14/10, in particular at pages 3-4). The Merck Manuals also explains how it was initially thought that tumor markers such as LDH would be useful to screen people for cancer, but that such markers are often present even in people without cancer, such that finding a tumor marker does not necessarily mean a

person has cancer (see page 2). The Merck Manuals also specifically cautions that LDH testing cannot be recommended for cancer screening (see table on page 4).

The teachings of Merck Manuals further indicate that elevation in the disease state is a necessary but not sufficient criterion for a marker to be used for the purpose of diagnosing the presence of the disease, since markers could be normally present in individuals without the disease or could be elevated for a variety of reasons, as in the case of LDH.

The teachings of the prior art therefore indicate that analytes that stem from or are induced by a pathogen may be non-specifically elevated in other clinical contexts, rather than being specific markers of the pathogen. In light of the prior art, therefore, one would not reasonably expect that any such marker could be used for the purpose of detecting a pathogen (i.e., diagnosing pathogen infection) without further study. For example, detecting LDH would be insufficient to detect HIV because LDH is not specific to HIV; levels can be elevated for a variety of reasons.

Moreover, the specification also fails to provide direction or guidance with respect to differential diagnosis. As such, one of ordinary skill in the art would not know, upon observing altered levels of LDH, whether to confer a diagnosis of HIV infection, cancer, etc. since levels would likely be altered in both of these diseases as well as in other contexts.

Furthermore, one skilled in the art would recognize that there is unpredictability associated with the clinical use of biomarkers even after a biomarker has been correlated with a specific disease state. For example, Bast et al. ("Translational Crossroads for Biomarkers" Clin Cancer Res 2005; 11(17), 6103-6108) point to the "lengthy process" of assay development and validation and note that many markers that correlate with disease statistically may not prove to

be useful clinically (p. 6105, right column). See also LaBaer et al. ("So, You Want to Look for Biomarkers" Journal of Proteome Research 2005; 4, 1053-1059), which teaches that crucial validation steps are needed to demonstrate that an identified biomarker is a reliable predictor, and also that the process of converting such a biomarker into a practical clinical test is even more daunting (p. 1053, see the paragraph bridging the left and right columns). Baker ("In Biomarkers We Trust?" Nature Biotechnology 2005; 23(3), 297-304) also speaks to the unpredictability involved in clinically applying biomarkers (see p. 298, the section "Walking on Thin Ice"):

> Using a new biomarker is like walking across a frozen lake without knowing how thick the ice is," says Ole Vesterqvist…"You start walking, and you get comfortable. Then you break through.

Thus, the state of the art teaches the unpredictability associated with the clinical use of biomarkers even after a biomarker has been correlated with a specific disease state. These references speak not only to the unpredictability associated with validating candidate biomarkers for clinical use, but also to the large quantity of experimentation involved in doing so.

Consequently, in order to carry out the claimed invention in its full scope, one of ordinary skill in the art would first have to identify the analytes that "stem from or are induced" by a given pathogen and then carry out research to determine which analytes are altered in a specific and sensitive manner upon pathogen infection. When taken together with the unpredictability associated with the process of marker identification and validation, as well as the lack of working examples of markers other than those that are proteins of a pathogen or antibodies specific to the protein, the specification fails to teach the skilled artisan how to carry out the claimed invention in its full scope without undue experimentation.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 44-45, 47-48, 73, 75-77, 81, 83-84, and 86-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Connor (US 5,627,026) in view of Osther et al. (U.S. 5,008,183).

O'Connor et al. teach a method of detecting a plurality of analytes, namely both an antibody to and an antigen of an infective agent, in a single sample aliquot. See the title, abstract; and column 1, line 58 to column 4, line 41. The infective agent may be FeLV, FIV, or HIV (column 4, lines 14-30) and simultaneous assessment of antigens and antibodies associated with the same viral infection (i.e. a pathogen) is clearly disclosed (column 4, lines 23-25).

The method of O'Connor et al. involves (a) providing a solid phase (solid support), which may be a non-porous material such as a microtiter well, or a glass, plastic, or latex bead (see especially column 3, lines 17-29; column 4, line 65; column 6, line 57 to column 8, line 3). An antigen capable of selectively forming an immune complex with a sample antibody (i.e., first analyte-specific receptor) is bound to the solid support at a first location, while an antibody capable of selectively forming an immune complex with a sample antigen (i.e., second analyte-specific receptor) is bound to the solid support at a separate position (see column 2, line 4 to column 3, line 7; and especially claims 1, 7, 9, and 14).

O'Connor et al. further teaches (b) contacting the sample with the solid phase and with detectable reagents. See column 3, lines 8-51, and claim 1 in particular. For example, O'Connor

et al. discloses the use of a labeled antigen (i.e., third receptor) that selectively binds to a captured antibody from the sample, together with the use of a labeled antibody (i.e., another third receptor) that selectively binds to a captured antigen in the sample in a method for detecting both antibody and antigen in a single sample (claim 1). The signals generated by the detectable labels are (c) separately measured or assessed (column 5, lines 43-47 and line 65 to column 6, line 6; and the claims, e.g. claim 1, step (e)).

Regarding the use of a test area-specific cutoff in step (c), O'Connor et al. exemplifies an ELISA test for FIV antibody in which non-FIV reactive feline serum was used as a negative control (see column 8, line 29 to column 9, line 25. Wells coated with FIV antigen (i.e., analyte-specific receptor) were incubated with the sample to be tested so as to allow antibody in the sample to bind to the FIV antigen (see especially column 8, lines 45-58). In the same manner, an antigen-coated well was also incubated with negative control serum. See column 8, lines 59-60. The signal (absorbance at 650 nm) due to this negative control was measured; any bound label measured in this case would be attributable to nonspecific binding since no analyte was present (i.e., the background signal in the absence of analyte). The presence of antibody to FIV is determined by relating the signal of the sample to the negative control signal. In particular, O'Connor et al. selected a cutoff of 3 times the absorbance signal due to the negative control sample, so that anything above this cutoff was regarded as a positive sample (see column 9, lines 20-25).

This means of interpreting assay results may be considered a “predetermined test area-specific cutoff”, since the negative control involved a duplicate well coated with the same analyte-specific receptor (FIV antigen) as in the test area well (the difference being that control

serum was used on the negative control well, while feline serum to be tested was used for the test area well). It is also clear from the teachings of O'Connor et al. that each well is *separately* assessed for signal. Furthermore, the reference makes clear that the absorbance intensity of each well was compared to the negative control. Likewise, in the embodiments involving a filter as the solid support, the reference makes clear that each *respective* sample spot is assessed in relation to a control spot in order to determine whether the assay results are positive (see column 5, line 48 to column 6, line 6). For all of these reasons, the negative control well of O'Connor et al. may be considered to be test area-specific. Moreover, the means of interpreting when the assay is positive or negative was *predetermined*, in that O'Connor et al. designated the cutoff level to be 3 times the absorbance signal of the negative control (as discussed above).

The O'Connor et al. reference differs from the claimed invention in that this use of a predetermined test-area-specific cutoff is only discussed in the context of the FIV antibody ELISA test, which involved only this single analyte and not a plurality of analytes. Although the reference elsewhere clearly teaches detection of a plurality of analytes, cutoff levels are not explicitly disclosed except in the example involving the FIV antibody ELISA. In other words, O'Connor et al. used a test area-specific cutoff to interpret the results of their assay, but only exemplify this type of data interpretation in an exemplary assay that determined a single analyte rather than a plurality of analytes.

O'Connor et al. therefore fails to specifically illustrate classifying the signal in *multiple* test areas (i.e., the first or second test area) as positive or negative by means of a "test area-

specific cutoff", since in the FIV antibody ELISA test exemplified there was only *one* type of test area.

At issue, therefore, is whether it would be obvious to also use cutoff levels to interpret the results of the assay in the same manner on <u>each type of test area</u> (i.e., in a "test area-specific" manner) when using <u>multiple</u> types of test areas to simultaneously assay both antigen and antibody according to the other disclosed embodiments of O'Connor et al.

However, as discussed in detail above, O'Connor et al. provides an example in which negative control serum is applied to an FIV antigen-coated well (i.e., a duplicate well coated with the same analyte-specific receptor as the test area). The results from this negative control are assessed to provide a cutoff that is then used to interpret the results from the test area. Since this control involves binding of negative control serum to FIV antigen, the same analyte-specific receptor that is on the test area, the control (and the resulting cutoff) may be said to be specific to the test area. See columns 8-9, "ELISA Test for FIV".

It is therefore clear that the negative control taught by O'Connor is specific to the particular analyte-specific receptor being assayed, and hence also to the particular analyte as well as to each test area.

Similarly, Osther et al. also relates to assays for detecting the presence of antibodies, and teaches that a negative control provides information about the absence of reactive antibodies in a sample that are specific to the particular analyte-specific receptor ("test antigen") that is being

used for the assay (see column 1, lines 19-61, especially at lines 47-61). A negative control also provides information as to the reaction level at which a specimen may be considered reactive: the cut-off point in a particular test is often based on the relative value obtained by a positive and/or negative control (ibid). The negative control value thus affects the specificity of the test system.

The teachings of Osther et al. therefore indicate that those of ordinary skill in the art recognized the value of negative controls in providing information about the particular analyte-specific receptor being used in assays to detect analytes (in this case, antibodies); as well as in establishing a cut-off point.

Therefore, although O'Connor et al. only discuss using a negative control and a cutoff in a particular example which involved only one analyte (FIV antibody), O'Connor et al. elsewhere clearly contemplate detecting multiple analytes in a single sample aliquot (see, e.g., the title).

In particular, as discussed in detail above, O'Connor et al. provides an example in which negative control serum is applied to an FIV antigen-coated well (i.e., a duplicate well coated with the same analyte-specific receptor as the test area). The results from this negative control are assessed to provide a cutoff that is then used to interpret the results from the test area. Since this control involves binding of negative control serum to FIV antigen, the same analyte-specific receptor that is on the test area, the control (and the resulting cutoff) may be said to be specific to the test area. See columns 8-9, "ELISA Test for FIV".

It is therefore clear that the negative control taught by O'Connor is specific to the particular analyte-specific receptor being assayed, and hence also to the particular analyte as well as to each test area.

The teachings of Osther et al. underscore the value of conducting control measurements for each analyte-specific receptor.

When scaling up to detect more than one analyte as directed by O'Connor, it would be obvious to employ negative control measurements to interpret the results of the assays for multiple analytes in the same manner. In other words, it would have been obvious to apply negative control serum to duplicate wells having not only FIV antigen-coated well, but also to duplicate wells coated with the other analyte-specific receptors specific to the other analytes under assay. For example, when detecting both FIV antibody and FIV antigen using wells coated with FIV antigen and FIV antibody, respectively, it would have been obvious to apply negative control serum to both FIV antigen-coated wells (as in the example of O'Connor) as well as to FIV antibody-coated wells.

Consequently, when simultaneously assaying both antigen and antibody according to the methods of O'Connor et al., it would have been obvious to one of ordinary skill in the art to measure the background signal due to a negative control sample for <u>each</u> type of test area (i.e., each different immobilized antigen/receptor on the solid phase) in a test area-specific manner because such negative control measurements were of recognized value in providing information about a <u>particular</u> test reagent for detecting an analyte (as taught by Osther et al.). For example, it

would have been obvious to select a cutoff of 3 times the absorbance signal due to the negative control sample (as taught by O'Connor et al.) for each respective test area and to designate test areas with a signal greater than cutoff as positive. Such a cutoff would be said to be a test area-specific cutoff based on a test area-specific background as claimed.

Motivation to combine the reference teachings in this manner comes from the teachings of Osther et al., which indicate that those of ordinary skill in the art recognized the value of negative controls in providing information about the particular test reagent used to detect the analyte of interest.

As such, when using multiple receptors to detect multiple analytes, one would be motivated to perform a negative control on each different receptor/ test area and use such test area-specific background measurements as the basis for determining whether each test area was positive or negative, by means of a test area-specific cutoff as in O'Connor et al.

Put another way, given that O'Connor et al. focus on the simultaneous determination of both antibody and antigen in a sample, it would have been obvious to one of ordinary skill to perform negative control background measurements for each immobilized receptor in the same manner exemplified for FIV antigen when using a plurality of receptors to detect both antigen and antibody analytes. Similarly, it would have been obvious to employ a test area-specific cutoff based on such negative control measurements--since different analytes are being detected in each different test area, the ordinary artisan would have found it obvious to relate the signal value of the sample to the signal value of a negative control sample for each receptor/ test area used. For example, when detecting FIV antigen in addition to FIV antibody, it would have been

obvious to include a negative control for FIV antigen and to relate the signal from an FIV antibody-coated well to the signal from the negative control, thereby measuring background due to non-specific binding.

Furthermore, it would have been obvious to apply the known technique for analyzing the results from each reaction (e.g., from each sample well) in the same manner as described for the FIV antibody. One would be motivated in light of the clear teaching of O'Connor et al. that this relation of sample signal to control signal allows for the validity of the assay to be determined. As such, it would have been obvious to calculate a cutoff for antibody as well as for antigen in order to determine whether the sample was in fact positive for the presence of each of these analytes.

With respect to claim 45 and 84, O'Connor et al. teach detection of both HIV antigen and anti-HIV antibody (column 4, lines 23-25). Hepatitis B (i.e., HBV) antigen is also contemplated (see column 4, lines 6 and 17 and claim 13).

With respect to claim 47 and 86, O'Connor et al. teach controls, e.g. control wells coated with receptor and to which positive or negative control sample is added (column 3, lines 26-29; column 5, line 48 to column 6, line 6; and column 8, lines 59-65). A negative control can be performed by coating spots with a non-specific antibody (column 5, lines 48-65). This is done to control for nonspecific reactions, i.e. "interferences".

With respect to claim 48 and 87, O'Connor et al. teaches detection reagents comprising a third receptor specific for the analyte (e.g., antibody or antigen specific for antigen or antibody,

respectively) bound directly to a signal-generating group (enzyme). See column 3, lines 8-51; column 7, lines 8-30 and 47-51; column 8, lines 50-56).

With respect to claims 73, 75 and 89, O'Connor et al. teaches detecting HIV p24 antigen and anti-HIV antibody (column 4, lines 23-30).

With respect to claims 76 and 90, O'Connor et al. teaches that the detectable labels may be enzyme labels (column 3, lines 47-51).

With respect to claims 77 and 81, O'Connor et al. teaches detection of Hepatitis B (i.e., HBV) antigen (see column 4, line 6) but fails to specifically teach detection of more than one analyte "derived from" HBV. Nonetheless, O'Connor et al. teach simultaneous assaying for antigens and antibodies associated with the same viral infection (column 4, lines 23-25). Although HIV and not HBV is exemplified in this context, it would have been obvious to one of ordinary skill in the art to select HBV from the finite number of viruses disclosed in the reference and to detect both HBV antigen in addition to anti-HBV antibody. One would be motivated to do this in order to assay for the presence of HBV virus.

11. Claims 46 and 85 rejected under 35 U.S.C. 103(a) as being unpatentable over O'Connor et al. in view of Osther et al. as applied to claims 44 and 83 above, and further in view of Ekins (US 5,837,551).

O'Connor et al. is as discussed above, which teaches test areas on non-porous solid supports such as microtiter plates. However, the reference fails to specifically teach that the test areas have diameters of 0.01 – 1 mm.

Ekins teaches forming arrays of “microspots” in which binding agents (i.e., receptors) are immobilized into defined, spatially separated test zones (i.e., “test areas”) on a solid support (column 2, line 35 to column 4 line 41). The microspots preferably have an area of less than 1000 square microns, e.g. 0.1 square mm, and can be for example of diameter 80 microns or 0.08 mm (column 3, lines 34-63; column 4, line 2). By providing such microspot arrays, a plurality of analytes may be simultaneously determined (column 3, lines 40-47). The microspots can be formed on a microtiter plate, i.e. non-porous support (column 7, lines 33-40). Binding of analytes to the binding agents immobilized in each microspot is then assessed using a detection agent capable of binding to the analyte and including a marker, e.g. an enzyme or fluorescent marker (column 3, lines 10-33).

Such miniaturized test zones contain small amounts of binding agent, allowing binding assays to be conducted with rapid kinetics to minimize the time needed to complete the assay (column 6, lines 4-8). In addition, less of the binding agent is necessary, diffusional constraints are reduced and assay sensitivity is also improved (column 6, lines 9-32).

Therefore, it would have been obvious to one of ordinary skill in the art to modify the method of O’Connor et al., Osther et al., and Bayer et al. (or alternatively O’Connor et al., Osther et al., and Tidey et al.) by depositing the first and second receptors into small test zones or “microspots” (e.g., of diameter 0.08 mm on a microtiter plate) as taught by Ekins et al. because detection of antibody and antigen could be conducted more rapidly and with greater sensitivity and would also require less of the capture reagents to be consumed.

When performing the prior art methods using microspots in this manner, it would have been further obvious to employ the detection scheme taught by Ekins to be suitable for the

microspot arrays, namely by using a detection agent capable of binding to analyte (i.e., third receptor) and including a marker capable of producing the signal for the assay.

12. Claims 82 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Connor in view of Osther et al. as applied to claims 44 and 83 above, and further in view of Miyamura et al. (U.S. 5,714,314).

O'Connor et al. and Osther et al. are as discussed in detail above. O'Connor et al. teaches simultaneous assay for antigens and antibodies associated with the same viral infection, e.g. HIV antigen and anti-HIV antibody, in order to rapidly screen blood or other biological fluids for infective agents such as HIV (see column 4, lines 14-30). The reference also mentions hepatitis in general, teaching how hepatitis antigen and anti-hepatitis antibody can be immobilized onto the solid support (to thereby detect hepatitis antibody and antigen, respectively). See column 2, lines 40-59 and column 3, lines 17-29). However, the reference fails to specifically teach detection of hepatitis C virus antigens or antibodies.

Miyamura et al. teaches that HCV was known in the art to be one type of pathogenic virus causing viral hepatitis. The reference further teaches that HCV was known as a grave infectious disease worldwide, and the prevention, early diagnosis, and treatment thereof were of recognized importance. See column 1, lines 30-44. Miyamura et al. also discuss how hepatitis C antigen can be used to detect antibody to HCV, e.g. in blood samples (abstract).

Therefore, it would have been obvious to one of ordinary skill in the art to select HCV (as taught by Miyamura et al.) as the type of viral infection to be screened in the method for simultaneous assay for antigens and antibodies associated with the same viral infection of

O'Connor et al. More particularly, it would have been obvious to employ anti-HCV antibody and HCV antigen as first and second receptors to detect HCV antigen and anti-HCV antibody, respectively, as the plurality of analytes. One would be motivated to do this because HCV was recognized as a disease of significant clinical concern, as taught by Miyamura et al. Motivation to combine the references also comes from the teachings of O'Connor et al., who teach detection of hepatitis in general albeit not the subtype of HCV.

One would have had a reasonable expectation of success because anti-HCV antibodies and HCV antigens were known in the art, as taught by Miyamura et al.

Response to Arguments

13. Applicant's arguments filed 4/5/2010 have been fully considered.

14. Regarding matters of Priority, the claims as currently presented are found to be supported by prior-filed foreign application No. 198 38 802.0, filed 8/26/1998. As a result, the rejections based upon the intervening Karl et al. reference have been withdrawn as discussed above.

Applicant's arguments with respect to priority to Application No. 198 27 714.8, filed 6/28/1998, have been fully considered (see Reply, pages 7-9) but are moot at this time, as no intervening reference is at issue.

15. Applicant's arguments with respect to the rejections of claims 44-45, 47-48, 73, 75-77, and 81 under § 103 as being unpatentable over O'Connor et al. in view of Osther et al. and either one of Bayer et al. or Tidey et al. have been fully considered (see Reply, pages 11-16) but are moot in light of the new grounds of rejection as set forth above. In particular, Applicant's arguments focus on the particular details of the Bayer et al. and Tidey et al. reference. However,

in light of the instant broadening amendments to the claims, the teachings of Bayer et al. and Tidey et al. are no longer necessary to the obvious analysis and have been omitted.

16. Applicant does not separately argue the limitations of dependent claims 46 or 82 (see Reply, pages 16-17).

Conclusion

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571)

272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641

/GAILENE R. GABEL/
Primary Examiner, Art Unit 1641

6/20/10